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AUREOMYCIN

Preliminary Report of a Clinical Trial

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INTRODUCTION

Aureomycin, a new antibiotic derived from the mold Streptomyces aureofaciens by Duggar[1] has been found to be active experimentally against certain viruses (notably the psittacosis-lymphogranuloma venereum group), some bacteria and the rickettsiae including epidemic typhus, murine typhus, scrub typhus, Rocky Mountain spotted fever, Q fever and rickettsial pox. This constitutes an unusual antimicrobial spectrum chiefly with reference to its virus and rickettsial activity both of which have hitherto failed to respond to antibiotics.

Aureomycin is readily absorbed after oral administration and produces no demonstrable toxic manifestations. The drug may also be given intramuscularly but produces a considerable amount of local pain and tenderness at the site of injection even when 1% novocaine is added to the diluent. Intravenous administration is not advisable. The optimal dose when the preferential oral route of administration is employed is not precisely known; however, a dose of 5 mgms. per kilogram every two to four hours has been recommended as a satisfactory dosage schedule in susceptible infections.

During the past three months (June to August) aureomycin has received a preliminary clinical trial at Children's Hospital and a total of 19 cases have been treated with the drug thus far. The type of cases and the response to aureomycin therapy are summarized as follows:

Disease	*Number of Cases*	*Response*
Rocky Mountain Spotted Fever	11	Excellent
Brucellosis	1	Improved
Staphylococcus Aureus Septicemia (Penicillin resistant)	1	?
Typhoid Fever	3	Poor
Miliary Tuberculosis	2	None
Rheumatoid Arthritis	1	None
Total	19	

Representative case reports and a brief resume of the efficacy of the drug in each group of cases are discussed below.

AUREOMYCIN IN ROCKY MOUNTAIN SPOTTED FEVER

J. M., a 13 year old white male, was admitted to Children's Hospital on July 30, 1948 under the care of Dr. Albert Orlosky with the complaint of fever of four days duration and rash of two days duration.

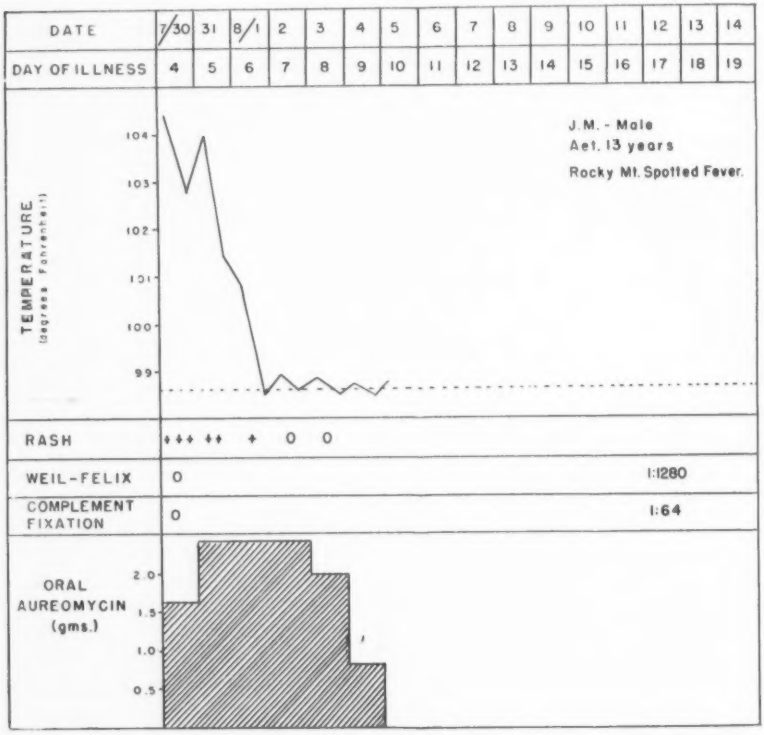

FIG. 1

The patient moved two ticks from himself two weeks prior to entry. He felt perfectly well when he went to camp two days later and continued in good health until four days before admission when he began to complain of headache and fever. A temperature of 102° was noted that day and during the next three days he received sulfadiazine; however, the temperature remained elevated, ranging between 102° and 104°. Two days after

the onset of fever, a rash was noted on his extremities and on the following day, had spread to his chest and abdomen. The patient's sister was in Children's Hospital at that time under treatment for Rocky Mountain spotted fever. Past history was non-contributory.

Physical examination revealed a well developed 13 year old white boy who appeared acutely ill. A reddish maculo-papular eruption which blanched on pressure was present over the entire chest, back, upper and lower extremities as well as the palms and soles. The remainder of the physical examination was essentially negative. The temperature on admission was 104.6°.

Laboratory examination revealed a hemoglobin of 10.5 gms. with 3.3 million red cells; the white cell count was 6,400 with 78% neutrophiles, 21% lymphocytes and 1% monocytes. The Weil-Felix agglutination test and the complement fixation test on July 30 at the time of admission were both negative. Two weeks later, however, the Weil-Felix agglutination titer had risen to 1:1280 and the complement fixation test performed at the National Institute of Health was positive in a dilution of 1:64.

Three hours after entry, aureomycin therapy was started. A dose of 300 mgm. of the drug was given hourly by mouth for three doses, then 200 mgm. every two hours thereafter. The temperature began to come down within 24 hours and after 48 hours was normal (Fig. 1). The child remained afebrile during the remainder of his hospital stay. The rash had completely disappeared by the fourth day. On the fourth day, the dose of aureomycin was reduced to 200 mgm. every four hours and the drug was discontinued after five days of therapy. The patient was discharged on the seventh day after an uneventful convalescence.

Discussion

The response to aureomycin in this case was eminently satisfactory with the rapid defervescence of temperature being matched by a striking clinical improvement. A similar dramatic response was observed in 10 other cases of Rocky Mountain spotted fever which have been treated with aureomycin during the summer of 1948; these cases will be reported in detail elsewhere.[2] In the eleven cases, the average duration of fever after initiation of the drug was two and one third days while the duration of the rash averaged four days. There were no complications and no mortality in this series and the patients were discharged after an average eight day hospital stay. Comparison with the 47 cases of spotted fever managed at Children's Hospital between 1931 to 1947 on either supportive therapy[3] or PABA[4, 5] would indicate that aureomycin is a considerably more effective agent against this disease and will undoubtedly become the drug of choice in the treatment of spotted fever.

AUREOMYCIN IN BRUCELLOSIS*

P. S., a 48 year old farmer, was admitted to Georgetown Hospital on July 26, 1948 under the care of Dr. W. Welsh with the complaints of progressive weakness of three years duration and intermittent fever.

The patient had been in good health until three years ago, at which time he began to complain of weakness and easy fatigability. Associated with this loss of energy, he experienced night sweats and frequent headaches. The fatigue and exhaustion had increased progressively with exacerbations and remissions during the course of the next three years accompanied by periodic fevers. One month prior to entry into the hospital, the patient again began to have chilly sensations and fever. An agglutination test for Brucellosis was positive in a dilution of 1:320 at this time. He was given penicillin for several days and the patient appeared to show some clinical improvement. However, his fatigue and weakness returned in one week and continued up to the point of complete exhaustion during the next fortnight. Four days prior to admission, the temperature rose to 104° and ranged between 102°–104° until the time of admission.

Past history revealed that the patient had had definite contact with Bang's disease in cattle. Three years prior to admission, there had been an outbreak of abortions among his cows; the patient, however, continued to drink raw milk freely.

Physical examination revealed a lethargic, disoriented white male who appeared acutely and chronically ill. Both his physical and mental reactions seemed unduly sluggish. The temperature was 102°, pulse 96, respirations 20 and blood pressure 100 systolic, 90 diastolic. Except for occasional basilar rales in the posterior lung fields, the physical examination was otherwise not remarkable.

Laboratory examination showed a hemoglobin of 15 gms. with a hematocrit of 46; the white cell count was 6,000 with 62% neutrophiles, 36% lymphocytes and 2% monocytes. Repeat urinalyses were essentially negative. Sedimentation rate was 38 mm. per hour. Febrile agglutination tests against the antigens of tularemia, paratyphoid A and B, typhoid and B proteus OX_{19} were negative. A blood culture taken at the time of admission grew out gram negative cocco-bacilli after ten days; these were identified as brucella organisms by Dr. Carl Larson at the National Institute of Health. An agglutination test for Brucella abortus was positive in a dilution of 1:640.

On the day following admission, the patient was started on oral aureomycin therapy. During the first 24 hours, he received 200 mgms. every two

* We are indebted to Dr. Jack Marland of the Georgetown University Hospital Resident Staff for his excellent cooperation in this case.

hours and thereafter was given 200 mgms. every 4 hours. The temperature began to come down by crisis during the next forty-eight hours and within three days, it had returned to normal and he remained afebrile during the remainder of his hospital course (Fig. 2). Concomitantly, a striking clinical improvement was noted. He began to feel considerably stronger and his sensorium cleared within five days after initiation of therapy. There was a noteworthy improvement in appetite and vigor and

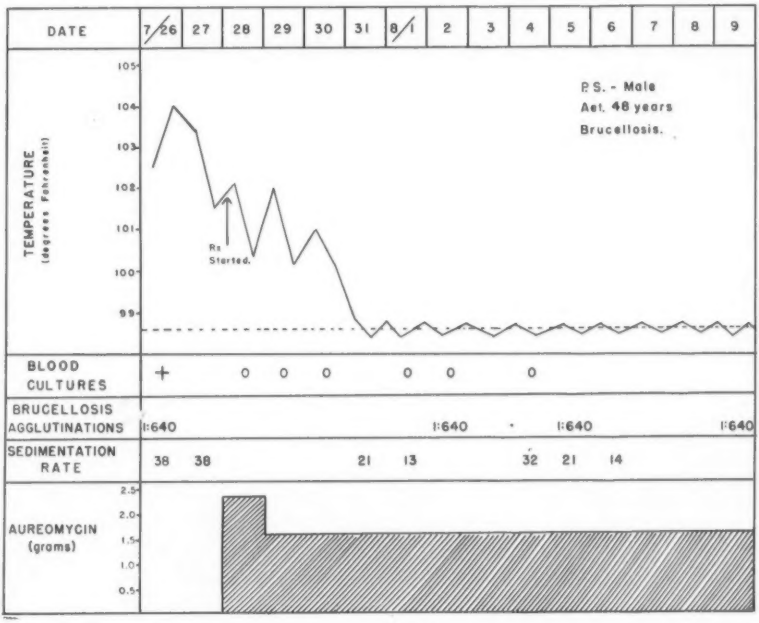

FIG. 2

within ten days the patient was ambulatory. Following initiation of therapy, six blood cultures were obtained within eight days and all were negative. No change was noted in the agglutination titer for brucellosis during the course of therapy; four agglutination tests taken at intervals during aureomycin treatment were all positive in a dilution of 1:640.

Aureomycin therapy was maintained for 14 days; during this time, the patient received a total of 18 grams. The drug was tolerated well and no untoward drug reactions were observed. The patient was discharged on the 16th hospital day.

Discussion

The case described here would probably fall in the category of chronic brucellosis with an acute exacerbation. Any evaluation of a therapeutic agent in chronic brucellosis would be singularly difficult in view of the fact that the course of the disease in its chronic form is punctuated by both sudden and gradual spontaneous remissions. It is possible that the striking clinical improvement in this patient following initiation of aureomycin therapy was more than mere coincidence. The positive blood culture obtained prior to therapy showed a cultural reversal within 24 hours after therapy was started and six consecutive negative blood cultures were obtained while the drug was being given. Similarly, the temperature came down by crisis within 48 hours after aureomycin was started and in the words of the patient he "felt better than he had in years." A two months follow-up on this patient (which is admittedly much too short) reveals that he has continued in good health since his discharge from the hospital.

An extensive clinical trial with aureomycin in acute brucellosis may show it to be a therapeutic agent of considerable promise. It is probable that the drug will be less effective in chronic cases in view of the propensity of the brucella organisms to lodge in focal areas such as the spleen, lymph nodes and gallbladder.

AUREOMYCIN IN TYPHOID FEVER

Case #1: R. H., a seven year old white male, was admitted to Children's Hospital on July 11, 1948 under the care of Dr. Robert Detwiler with the history of fever and anorexia of seven days duration.

The child had been in good health until one week before admission at which time he began to run a temperature and experienced some malaise. Concomitantly, he became anorexic and listless. During the next week on up to admission to the hospital, his fever persisted with the evening temperatures usually reaching 103°. There were no attendant chills, vomiting, diarrhea, pain or dysuria. The past history was not contributory.

Physical examination revealed a well developed child who appeared in no acute distress. Pertinent findings included a definitely palpable spleen on deep inspiration and a liver which could be readily felt two finger-breadths below the right costal margin. There were several discrete macular skin lesions diffusely scattered over the chest and abdomen having the appearance of rose spots. A grade II apical systolic murmur with maximum intensity just to the left of the sternum in the fourth interspace was present on auscultation. The temperature was 103.2°, pulse 110 and respirations 28. Physical examination was otherwise not remarkable.

Laboratory examination revealed a hemoglobin of 11.5 gms. with 3.8

million red cells; the white cell count was 8,000 with 70% neutrophiles, 26% lymphocytes and 4% monocytes. The urinalysis was negative. A heterophile agglutination test was negative. The agglutination test with E. typhosa (0 antigen) was positive in a dilution of 1:640. Four consecutive stool cultures taken within the first five days after hospitalization were positive for E. typhosa. Repeated blood and urine cultures were negative.

During the first four days after admission, the temperature showed a daily fluctuation ranging between 100° to 104°. On the fifth day aureomycin therapy was initiated; the drug was given in a dosage of 200 mgms. every two hours orally (approximately 8 mgms. per kilogram of body weight) and 20 mgms. every 12 hours intramuscularly. With the exception of an occasional dose vomited during the first 48 hours, the drug was well tolerated by mouth. After intramuscular administration, some local pain and tenderness at the site of administration was encountered; this was ameliorated to some extent when 1% novocaine was added to the distilled water used as a diluent.

Within two days after aureomycin was started, the temperature came down rapidly to normal and the patient appeared to be doing well clinically (Fig. 3). After 36 hours of normal temperature, a daily afternoon fever (up to 100°) was observed during the remaining nine days in the hospital. Ten daily consecutive stool cultures were negative after aureomycin was started and three blood cultures were similarly negative.

On July 23, the dosage of aureomycin was changed to 200 mgms. every four hours orally and two days later the dose was further reduced to 100 mgms. every four hours. On July 27, the drug was discontinued after 13 days of therapy. A total of 21.5 gms. orally and .48 gms. intramuscularly had been administered during this interval.

The patient was discharged on July 27 after a seventeen day hospital stay. A follow-up stool culture obtained one week later was negative for E. typhosa. However, six weeks later, a repeat stool culture again grew E. typhosa. No concomitant exacerbation of symptoms has been observed.

Case #2: S. H., a 23 months old colored female, was admitted to Children's Hospital on August 9, 1948 with the complaints of fever and anorexia of one weeks duration.

The child had been in good health until seven days prior to admission at which time she began to run a temperature elevation and shortly thereafter refused her feedings. The fever continued ranging between 101° to 104° and three days after the onset, she was seen by her local physician. Three intramuscular injections of 300,000 units of penicillin in oil and beeswax were given on consecutive days but there was no perceptible clinical improvement nor defervescence of temperature; hospitalization was therefore advised.

Past history and family history were non-contributory.

Physical examination revealed a somewhat drowsy, hyperirritable girl who appeared acutely ill. The temperature was 104°, pulse 100 and respirations 28. Pertinent findings included a mildly injected pharynx, a slight degree of nuchal rigidity, a distended and tympanitic abdomen and a liver which was palpable 2 cm. below the right costal margin. The spleen was not felt. Physical examination was otherwise negative.

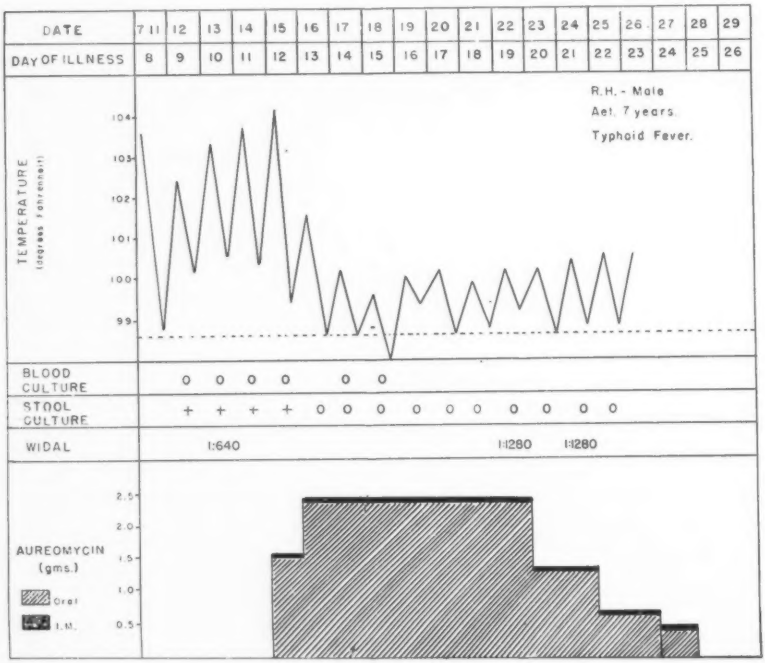

FIG. 3

Laboratory examination showed a hemoglobin of 11.5 gms. with 3.9 million red cells; the white cell count was 9,400 with 64% neutrophiles, 35% lymphocytes and 2% monocytes. Urinalysis was negative. Non-protein nitrogen was 30.4 mgm.% and the CO_2 was 54 vols. per cent. Spinal fluid examination was negative. An x-ray of the chest was normal. The agglutination test with E. typhosa (0 antigen) was positive in a dilution of 1:320. A stool culture on admission was negative; however, blood cultures taken on August 11th and August 12th (3rd and 4th days after admission) were both positive for E. typhosa.

Polymyxin B (aerosporin) therapy was started on the third day after hospital admission; the dosage was 20 mgms. every four hours orally (approximately 2 mgms. per kilogram of body weight) and 5 mgms. every 4 hours intramuscularly (about 0.5 mgms. per kilogram per dose). A polymyxin sensitivity determination was performed on the organism isolated from the blood culture and was found to be inhibited in a concentration of .02 micrograms per ccm. The polymyxin blood levels obtained at this time ranged between 1.4 to 2.1 micrograms. Blood cultures became

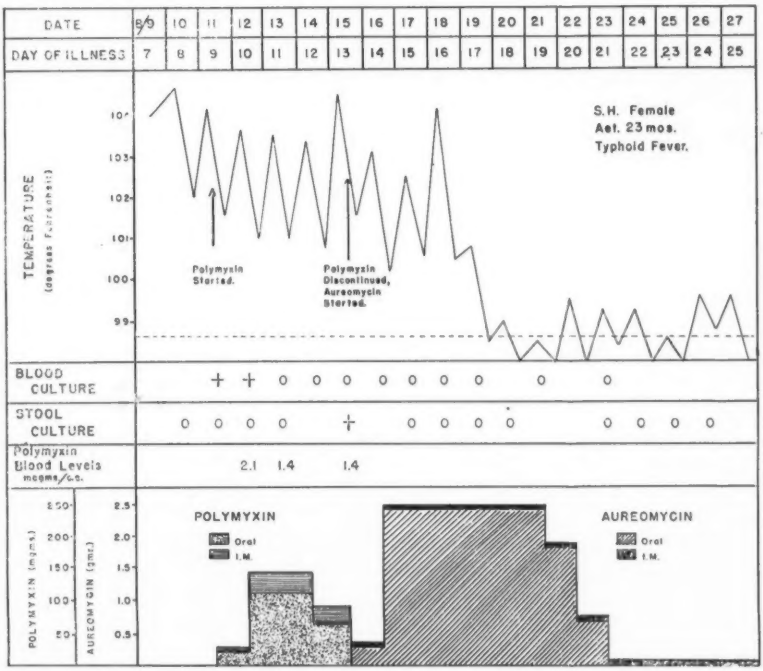

FIG. 4

sterile after the third day on polymyxin B and remained negative on nine consecutive cultures taken over the course of the next eleven days. A positive stool culture was noted on August 15th but eight consecutive negative stool cultures were obtained thereafter. Daily urines obtained while on polymyxin B therapy showed no albuminuria or white cells. Similarly, there was no increase in the blood non-protein nitrogen.

In spite of the bacteriological changes which might be attributed to polymyxin B therapy, no clinical improvement was perceptible and the

child remained drowsy and toxic with the temperature fluctuating between 101° and 104° daily (Fig. 4). Vigorous supportive measures were required including continuous intravenous infusions of crystalloid fluids, plasma and four blood transfusions.

In view of the relatively disappointing response to polymyxin B clinically, the drug was discontinued after five days of therapy and aureomycin was substituted. The latter drug was given in a dose of 200 mgms. every two hours by mouth (20 mgms. per kilogram of body weight) and 20 mgms. every 12 hours intramuscularly. During the next four days after the initiation of aureomycin therapy the temperature continued to show a daily fluctuation between 101° and 104° in spite of negative blood and stool cultures, and the child remained acutely ill. On August 20th (18 days after the onset of illness), the temperature came down by lysis and a gradual clinical improvement ensued The abdominal distension disappeared and the patient's appetite improved. The stools which had been diarrheal in consistency during the first ten days in the hospital became less frequent and showed some formed element.

Oral aureomycin therapy was discontinued on August 23rd (after eight days) and the intramuscular administration of the drug was discontinued four days later.

During the last week in the hospital the child did quite well although a low grade temperature elevation (up to 100°) was noted every afternoon. The patient was discharged on August 27th after a nineteen day hospital stay.

Case #3: E. M., an eight year old colored female, was admitted to Freedman's Hospital under the care of Dr. W. W. Cardozo on August 18, 1948 with the complaints of fever and malaise of five days duration and diarrhea of one day duration.

The child had been in good health until five days before admission at which time she began to complain of a severe headache and abdominal pain. Shortly thereafter she vomited several times and started to run a temperature elevation. The abdominal pain was rather vague without any definite localization. She became drowsy and anorexic on the following day and the fever persisted. Sulfadiazine was started at this time but no perceptible clinical improvement nor subsidence of fever was observed during the next two days. On August 17, one day prior to admission, the patient began to have diarrhea accompanied by a moderate degree of tenesmus and during the course of the day, passed about 15 to 20 watery greenish bowel movements. No blood was noted in the stools.

The patient had not been out of Washington recently and no other members of the family had experienced any diarrhea. She had visited a neighborhood swimming pool daily during the week prior to the onset of illness.

Physical examination revealed a well developed lethargic girl who appeared acutely ill. The temperature was 103.2°, pulse 120 and respirations 24. The tongue was dry and coated and the pharynx was mildly injected. There was a moderate degree of abdominal distension but no direct or rebound tenderness was elicited. The spleen was readily palpable on deep inspiration. No rose spots were discernible. The physical examination was otherwise negative.

Laboratory examination showed a hemoglobin of 10 gms. with 3.1 million red cells; the white cell count was 6,000 with 53% neutrophiles, 41% lymphocytes and 6% monocytes. Urinalysis was negative. The sedimentation rate was 40 mm. per hour and the hematocrit was 27.5. Kahn and Wasserman were negative as was a heterophile agglutination test. A throat culture revealed Streptococcus viridans and Staphylococcus albus, while a urine culture grew out E. coli. Agglutination tests for typhoid, paratyphoid, brucellosis and tularemia were negative; the Weil-Felix agglutination test with Proteus OX_{19} was positive in a dilution of 1:40; however, complement fixation tests for Rocky Mountain spotted fever and endemic typhus performed at the National Institute of Health were both negative. Two separate blood cultures taken on the day of admission both grew out Eberthella typhosa and subsequent repeat daily blood cultures were similarly positive. Stool cultures on Endo and bismuth sulfite media revealed no pathogens.

On the day of admission before the results of the blood cultures were known, the patient was started on penicillin. She continued to run a septic temperature ranging between 101° to 105° and the diarrhea continued unabated She appeared progressively drowsy and toxic and required supportive intravenous crystalloid fluids, plasma, blood and antipyretics. On August 23, when the diagnosis of typhoid fever became apparent, penicillin was discontinued and the child was started on aureomycin therapy; the initial dose was 200 mgms. every two hours orally during the first day and then 100 mgms. every three hours thereafter (approximately four mgms. per kilogram of body weight per dose). Concomitantly the patient was given five mgms. of aureomycin every eight hours intramuscularly. The drug was well tolerated. No perceptible clinical nor bacteriological effect from the drug was noted however. The temperature continued to run a septic course ranging between 98° to 106° and there was no singular improvement in the appearance of the patient nor of the stools (Fig. 5). Daily blood cultures taken while on aureomycin therapy continued to grow out Eberthella typhosa, seven consecutive cultures being positive from August 24 to August 30. Four stool cultures obtained during this interval revealed no pathogens. On August 30 when it had become apparent that the aureomycin was exerting no favorable effect on the course of the disease,

it was discontinued; during the eight day interval of aureomycin therapy, the patient had received 6.8 gms. orally and .12 gms. intramuscularly.

On the following day (August 31), polymyxin B (aerosporin) was started; the dose was 30 mgms. every four hours orally and 20 mgms. every six hours intramuscularly. During the next five days, no detectable clinical improvement ensued; the temperature continued to spike daily ranging between 100° to 104° and the child remained moderately toxic. The blood cultures which had been consistently positive while on aureomycin became

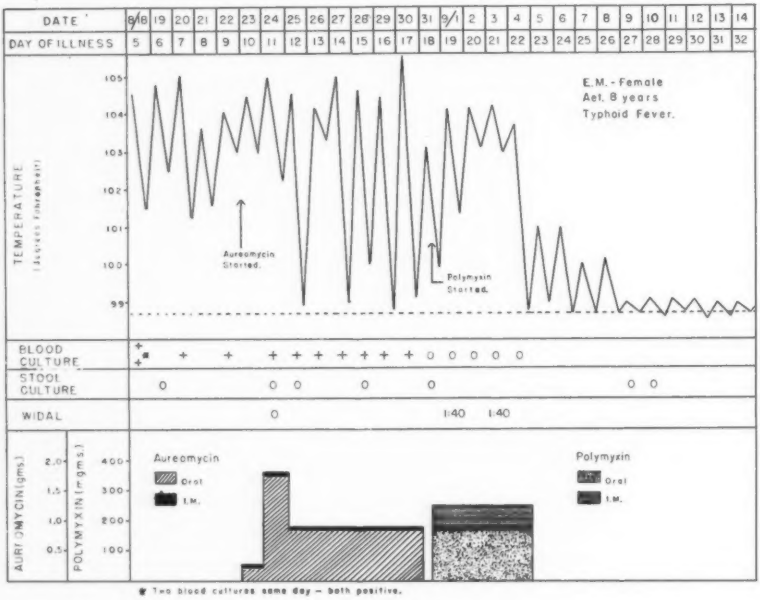

FIG. 5

negative for the first time on August 31 coincident with the initiation of polymyxin B therapy and five consecutive negative blood cultures were obtained from August 31 to September 4 during the interval of polymyxin B administration. Stool cultures remained consistently negative. Urinalyses obtained during polymyxin B therapy showed no evidence of albuminuria.

Persistence of a septic temperature prompted a discontinuation of polymyxin B after five days of therapy during which time 900 mgms. orally and 400 mgms. intramuscularly had been given. Within the next three days the temperature came down to normal by lysis and the patient re-

mained afebrile during the remainder of her hospital stay. The child was discharged on September 14, after a 28 day hospital stay.

Discussion

The results with aureomycin in typhoid fever were not at all conclusive in view of the fact that only three cases were treated. However, it permitted some preliminary impressions, the correctness of which must await further clinical trial on a large number of cases.

In case #1 (R. H.), there was some indication that the drug produced a favorable effect on the course of the disease during the acute phase. The temperature which had been ranging between 100° to 104° prior to the administration of the drug came down to normal within 48 hours and the stools which had been positive for E. typhosa on four consecutive cultures prior to therapy became negative on the day following administration of aureomycin and remained negative on ten consecutive cultures thereafter. It should be pointed out that the temperature did rebound slightly after the initial defervescence and continued during the next 10 days in low grade fashion. There remains the possibility that the initiation of aureomycin on the 12th day of the disease may have coincided with the spontaneous defervescence of temperature not infrequently seen in the pediatric age group with typhoid fever at the end of the second week in untreated cases. The recurrence of positive stool cultures after six weeks with the production of the carrier state would be in keeping with this latter premise.

In Case #2 (S. H.), both polymyxin B (aerosporin) and aureomycin were used consecutively and the efficacy of either one of these new antibiotics was not striking clinically. The temperature continued to fluctuate between 100° to 104° daily throughout the entire course of polymyxin B therapy (5 days) and aureomycin administration (8 days). The duration of the fever was 18 days which was not in any sense less than the duration of fever in the untreated case of typhoid fever in a child. The patient remained acutely ill during the entire phase of therapy and one could not say that the clinical course of the disease was effected favorably in this case by either polymyxin B or aureomycin.

In case #3 (E. M.), aureomycin was manifestly disappointing both bacteriologically and clinically as a therapeutic agent. The blood cultures remained consistently positive while on therapy and the temperature continued to spike daily during the eight days of aureomycin administration. Similarly, there was no striking clinical effect resulting from the administration of polymyxin B which was maintained for 5 days after aureomycin was discontinued. The child ran a temperature for 21 days and then defervesced by lysis which again would be the average duration of temperature elevation in an untreated case of typhoid fever.

In summary, it would be our opinion that aureomycin did not produce any perceptible reduction in the duration of illness in the typhoid cases #2 and #3 while in case #1 there might have been some favorable effect exerted on the course of the disease during the acute phase by the drug. Similarly polymyxin B was not too impressive as a therapeutic agent in the two cases of typhoid fever in which it was used. It would appear that both of these new antibiotics have shown up to much better advantage in vitro than in vivo in cases of typhoid fever in precisely the same fashion as streptomycin. Further clinical trials in typhoid fever of these antibiotics as well as chloromycetin will be awaited with interest.

Penicillin resistant staphylococcus septicemia

treated with aureomycin

D. L. S., an 8 year old white female admitted to Children's Hospital on August 26, 1948, was found to have a Staphylococcus aureus septicemia with the blood culture obtained on admission containing 275 colonies per ccm. Large doses of penicillin were administered over the course of the next week (up to 4 million units per day). However, the four blood cultures obtained during this interval remained positive for Staphylococcus aureus in spite of a penicillin blood level of 10 units/cc. On September 3rd the dose of penicillin was increased to 12 million units per day and streptomycin was initiated in a dose of .5 gms. every 8 hours. In spite of this intensive therapy, the blood cultures remained positive during the next 4 days (the colony counts ranging from 112 to 125 per ccm. of blood) and the temperature continued to fluctuate between 101° to 105°. On August 7, the sensitivity of the organism was found to be 7.5 units per ccm.

In view of the critical condition of the patient, the poor response to massive doses of penicillin and the marked resistance of the organism, it was considered advisable to institute heroic therapeutic measures. Thus on September 8th, the dose of penicillin was increased to 24 million units per day and on September 9th, aureomycin therapy in a dosage of 200 mgms. orally every 2 hours was initiated. Simultaneously, sulfadiazine was also started. Within 12 hours, there was a striking drop in temperature to 99° and during the next 48 hours, the temperature fluctuated between 99° and 100°. Four blood cultures obtained during the next 7 days were all negative. In view of the nausea and vomiting which this patient continued to have, all oral medication including the aureomycin and sulfadiazine was discontinued after 5 days and the child remained on intramuscular penicillin. At the time of writing, the patient has developed a severe nephritis with marked azotemia, albuminuria, hypertension and edema and her prognosis is eminently poor. However, the blood cultures have remained persistently negative for 2 weeks.

Discussion

It would be manifestly difficult to calibrate the role that aureomycin played in sterilizing the blood cultures in this case. The child had a staphylococcus septicemia with a markedly penicillin resistant organism (7.5 units per cc.) The organisms were probably arising from a focus in the endocardium. During the first 2 weeks of therapy, over 100 million units of penicillin was administered and yet the blood cultures remained positive for Staphylococcus aureus. On August 10th the temperature dropped precipitously to normal and the blood cultures became sterile within 12 hours after aureomycin and sulfadiazine were started and within 24 hours after the dose of penicillin was doubled from 12 million to 24 million units. Which of these measures produced the cultural reversal is difficult to say. It would have been of singular interest to have used aureomycin alone at this junction; however, the child was so critically ill that it was not deemed expedient to have discontinued the penicillin.

In vitro studies have shown that staphylococcus organisms are inhibited in a concentration of aureomycin up to .6 micrograms per ccm.[6] This concentration could be very readily achieved with the dose of aureomycin used in this case. There is a possibility that aureomycin produced the sterilization of the blood stream in this patient and it would be of considerable interest to try the drug alone in future cases of penicillin resistant staphylococcal infections.

MILIARY TUBERCULOSIS TREATED WITH AUREOMYCIN

Two cases of miliary tuberculosis in infants under one year of age were treated with aureomycin in doses ranging from 10 to 15 mgms. per kilogram every 4 hours. No improvement was observed in either case. One infant died within 2 weeks and the other case has remained critically ill at the present writing. In both instances, the disease was well advanced at the time of initiation of aureomycin therapy.

There is evidence of in vitro activity by aureomycin against M. tuberculosis and further clinical trials in other types of tuberculosis are indicated.

RHEUMATOID ARTHRITIS TREATED WITH AUREOMYCIN

One case of rheumatoid arthritis was treated with aureomycin. No salutary effect from the drug was noted.

TOXICITY OF AUREOMYCIN

Thus far no systemic reactions resulting from aureomycin administration have been encountered. In our cases, an occasional child had some nausea and vomiting during the first 24 to 48 hours after initiation of therapy but

the drug was tolerated extremely well. No allergic manifestations were noted. Following intramuscular injection, local pain and tenderness was observed at the site of injection but no sloughing or necrosis ensued.

A study was performed on 5 children selected at random from the ward. Three were infants weighing between five to seven kilograms and the other two were older children weighing 26 and 27 kilograms. Aureomycin in a dosage of 5 mgms. per kilogram of body weight was given orally every 2 hours for seven days and several pertinent laboratory tests were performed referable to the liver, kidney and hematopoietic systems and included the following:

Kidney	*Liver*	*Hematopoietic*	*Miscellaneous*
Urine	Cephalin flocculation	Hemogram	Carbon dioxide combining power
Non protein nitrogen	Van den Bergh	Platelet count	
	Prothrombin time	Reticulocyte count	
	Blood sugar	Bleeding time	
		Clotting time	
		Fragility test	

These laboratory determinations were performed on each patient prior to administration of the drug as a control and then repeated on the third, sixth and ninth days after aureomycin was started.

It was found that no significant changes were encountered in any of these laboratory tests obtained on these children during the interval the drug was given.

If one is permitted to hypothesize from past experience with the other antibiotics such as penicillin, streptomycin, polymyxin and bacitracin, it would be logical to suppose that aureomycin will eventually be found to produce some untoward effects when a wider experience with the drug has been accumulated. However, at the present writing, none has been observed.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: Edwin Vaden, M.D.
D. Joseph Judge, M.D.
By Invitation: Bernice Wedum, M.D.

Edwin Vaden, M.D. R. M. 44–7316

This patient, a white female infant, had two admissions to Children's Hospital, the first at nine days of age and the second at four months of age. The data obtained on the two admissions is as follows:

First Admission: At nine days of age the patient was transferred from the hospital where she was born because of intermittent attacks of dyspnea of about six hours duration. Also, there was a history of paroxysmal cyanosis present since birth. The baby weighed 7 pounds 5 ounces at birth. The pre-natal course had been uneventful and delivery had followed a spontaneous onset of labor at term. The infant was breast fed. Family history was non-contributory.

Physical examination revealed a well-developed and nourished white female infant, weighing 7 pounds 5 ounces. The patient became cyanotic when crying. Both fontanelles were open, but appeared normal. The remainder of the physical examination revealed no abnormalities except for the chest findings, which indicated the point of maximal impulse of the heart to be at the left border of the sternum. The rate was rapid and the heart sounds were said to be louder on the right than on the left of the sternum. A systolic murmur was present and was audible over the entire precordium.

The urinalysis was normal. The hemoglobin was 13 gms., (erythrocyte count not recorded). The leucocyte count was 10,700 with a differential of 45 percent neutrophiles, 51 percent lymphocytes, 2 percent monocytes, 1 percent eosinophiles, and 1 percent basophiles.

A chest x-ray revealed the heart to be somewhat displaced to the right and to have a very irregular contour, which was said to be suggestive of congenital heart disease. However, a supracardiac shadow was noted to be present bilaterally, and since thymic enlargement could not be ruled out, irradiation of the thymus was suggested. Re-examination after x-ray therapy showed the supracardiac shadow to have undergone marked reduction in size, but the heart was still noted to be displaced to the right. An electrocardiogram was done and revealed a sinus tacycardia with a rate of 160. The PR interval was 0.12 seconds. In lead I the P, QRS, and T waves were inverted. The P and T waves were upright in lead II and III; the QRS complex was "mostly inverted" in lead II, and was

"diphasic and mostly inverted" in lead III. There was a low voltage of the QRS complex in all leads. (Fig. 1)

Her treatment was symptomatic and her hospital course was uneventful. She was discharged on the 17th hospital day, weighing 7 pounds, 7 ounces.

Second Admission: At four months the patient was re-admitted to the hospital because of a cold and fever. She was said to have had no attacks of cyanosis since discharge, but there was a history of shortness of breath after crying. The present illness had its onset two nights before admission when she began coughing up phlegm and running a fever. She was very fretful all night and the following morning began to vomit. Her symptoms persisted until the day of admission, when her temperature rose to 105 degrees F. Her appetite had been good until this time when she seemed to have difficulty in swallowing and vomited after each feeding.

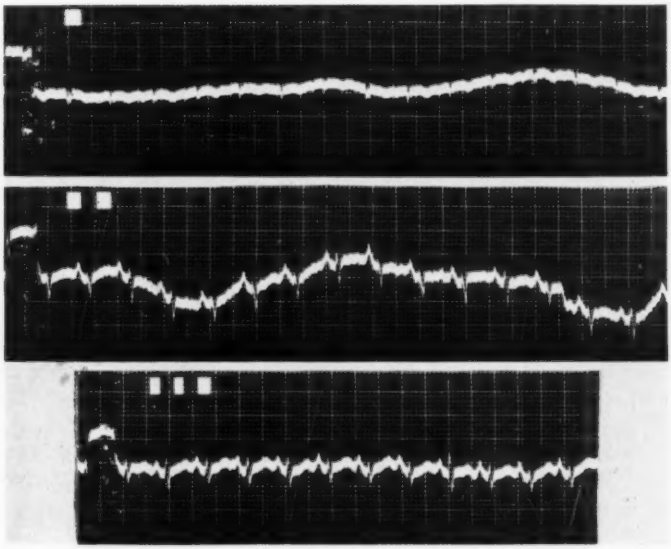

FIG. 1. R. M. Electrocardiogram taken upon admission

Physical examination revealed an acutely ill, apathetic patient with a temperature of 105°F., weighing 10 pounds 8 ounces. There were no petechiae noted. The lips were dry, but not cyanotic. The tongue was rather cyanotic and dry and the pharynx and tonsils were quite red. The heart was said to be enlarged to the left anterior axillary line and on the right to the midclavicular line. The PMI was at the right of the sternum,

rather than to the left. There was a loud harsh systolic murmur heard best to the right of the midline from the second to the fifth interspaces. The rate was rapid. The liver was palpable 3 cm. below the right costal margin, the surface being smooth and non-tender. The remainder of the physical examination was normal.

A chest x-ray was done and there was no evidence of pathology of the lung parenchyma; the heart was noted to have the contour of a dextrocardia without situs inversus.

The patient was put on sulfonamides and her temperature fell by lysis to 100°F. on the fourth day where it remained until about the eighth day when it suddenly rose to 104°F. and she expired. The pulse varied from 100 to 160 during her stay and her respiratory rate varied from about 20 to 30 per minute.

DISCUSSION

Bernice Wedum, M.D.: Before discussing this particular case, I am going to say a few words about the differential diagnosis of congenital cardiac malformation in children under the age of two years. It is my hope that you will carry away an idea of the methods one uses in approaching a case of this kind. For the points brought out in the following discussion I am entirely indebted to Dr. Helen B. Taussig's book "Congenital Malformation of the Heart" and to a brief period spent in her clinic.

There are eight basic questions that one first seeks to answer with information gained from the history, physical examination, hemoglobin, red count, hematocrit, and in some cases arterial oxygen saturation, fluoroscopic examination in the antero-posterior, left anterior oblique, and right anterior oblique positions with barium swallow, x-rays, and electrocardiogram including unipolar leads. Other special studies such as angiocardiography and catheterization studies are not ordinarily done in children this young. Even when such studies are done one is still seeking the answer to the eight questions listed below.

1. What chambers or vessels are enlarged or diminished in size?
2. Is the blood supply to the body adequate or altered as to nutrition or oxygen?
3. Is the blood supply to the lungs adequate, diminished or excessive?
4. Are the great vessels both present and in normal relationship? Their branches?
5. Is a venous arterial shunt present?
6. Is an arterio-venous shunt present?
7. Is the venous return to the heart normal?
8. Is heart failure present?

Every procedure in the study of the child must be carefully and ac-

curately done. For example, it is useless to carry out a fluoroscopic examination unless the eyes are thoroughly accommodated. The evaluation of the presence or absence of cyanosis is sometimes difficult and only arterial oxygen studies will establish whether or not reduced hemoglobin is reaching the peripheral circulation through a venous arterial shunt. If at all possible, auscultation of the heart should be carried out while the child is sleeping or resting quietly in his mother's arms. A systolic murmur is usually present in congenital malformation and its nature in infants is of no special significance. One is more interested in the character of the second sound. If it is strikingly pure it gives evidence that one of the great vessels is stenosed or atretic since only one set of semi-lunar valves is closing. Normally the second heart sound is split.

When all clinical information has been carefully assembled and the answers to these eight questions obtained as completely as possible a certain statistical sense of the relative frequency of these malformations and combinations of malformations must be brought to bear on the problem. The malformations which must be first considered in an infant under two years of age who has had episodes of cyanosis, are four in number and convenient to remember since they all begin with the letter T.

1. Transposition
2. Tetralogy of Fallot
3. Tricuspid atresia
4. Truncus arteriosus.

Other malformations which are far less common but which must be considered are single ventricle with rudimentary outlet chamber, extreme dextroposition of the aorta with pulmonary atresia or stenosis, Taussig transposition, pure pulmonic stenosis, anomaly of the venous return and anomalous origin of the left coronary artery from the pulmonary artery.

Infantile coarctation is always a possibility but is usually combined with another malformation which obscures its presence.

Infants with aortic atresia are born with enlarged heart and usually die during the first few days of life.

For the sake of completeness the following anomalies are listed.

Interauricular septal defects
- Patent ostium primum
- Patent ostium secundum
- Common atrioventricular canal

Patent Ductus Arteriosus
Interventricular Septal Defect
Adult Type Coarctation
Eisenmenger Complex

These last malformations will not be discussed since they do not enter into the diagnosis in this particular case.

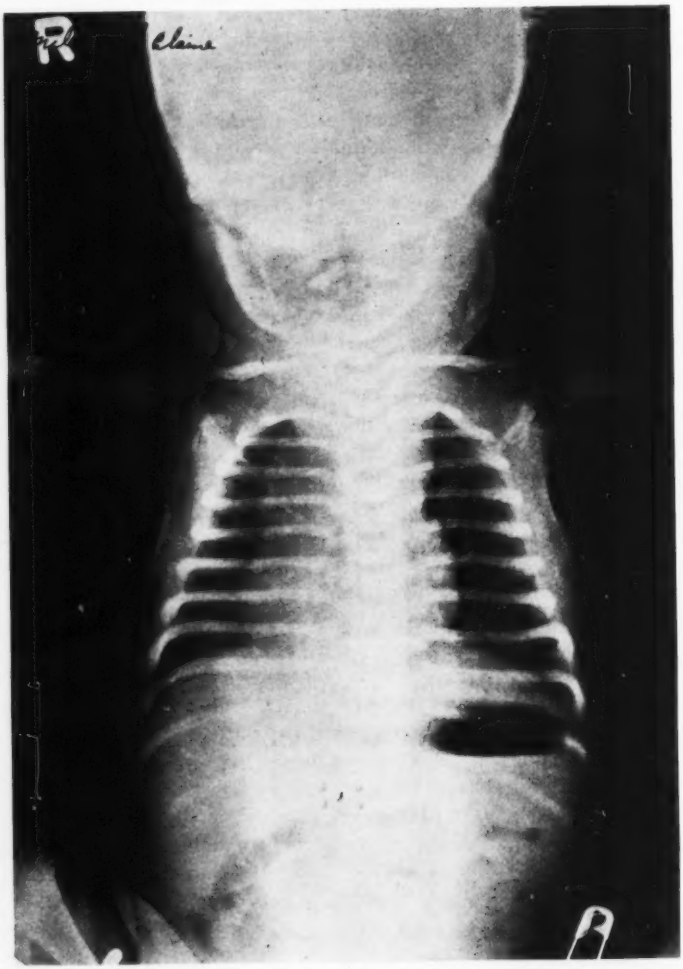

FIG. 2. R. M. X-ray taken upon admission showing a grossly abnormal cardiac contour which probably represents thymic gland enlargement.

To summarize, there are two avenues of approach to a case of this nature; the first based on information gained by careful clinical and laboratory observations, and the second based on statistical considerations.

The case presented today is essentially that of a baby with a severe congenital malformation who died at the age of four months of cerebral anoxemia. I am going to begin by throwing the thymus gland out of the picture. The baby was first admitted because of attacks of paroxysmal dyspnea. This type of dyspnea is caused by cerebral anoxemia and not by pressure of an enlarged thymus gland. Since the presence of cyanosis was mentioned by two separate observers it may be assumed that cyanosis was actually present. It is well known that five grams of reduced hemoglobin must be present in the peripheral circulation before cyanosis first becomes visible and since this baby had thirteen grams of hemoblogin it is reasonable to assume that almost half the circulating blood was venous. The episodes of paroxysmal dyspnea also support this conclusion.

The presence of a loud systolic murmur confirms the existence of a congenital malformation. The description of the point of maximal impulse at the left sternal border leads one to believe that one is dealing with an uncompletely rotated heart. The electrocardiogram, however, is characteristic of a mirror dextrocardia. One would not expect this type of tracing in an incompletely rotated heart. Either there is some error in the clinical observation or an error in reading the electrocardiogram.

Examination of the x-ray reveals the heart to be on the right and the stomach on the left. There are two electrocardiograms both showing inversion of all complexes in lead I. The clinical observation of the point of maximal impulse is apparently in error and one can begin by saying that the baby had a mirror image dextrocardia without situs inversus. The electrocardiogram and x-rays give further information which will be discussed later.

The child apparently did well until she had an upper respiratory infection. Although she was said to have had no attacks of cyanosis since discharge I honestly do not believe this. I wonder if a red count or hemoglobin was done at the time of the second admission?

Dr. Vaden: None was recorded.

Dr. Wedum: It is significant that the baby had gained three pounds during the first four months of life. This is fairly good evidence that the nutrition to the body was adequate and that a large amount of blood was not being shunted away from the peripheral circulation and recirculated through the lungs as occurs for example in a very large auricular septal defect.

The clinical description of the heart as being enlarged on the second admission is not borne out by the x-ray. The heart is normal in size in the anterior posterior position. Whether relative enlargement of the left or right ventricles is present cannot be determined without oblique views.

A liver palpable three cm. below the costal margin is not unusual in a baby this age. The respirations are a far more accurate indicator of con-

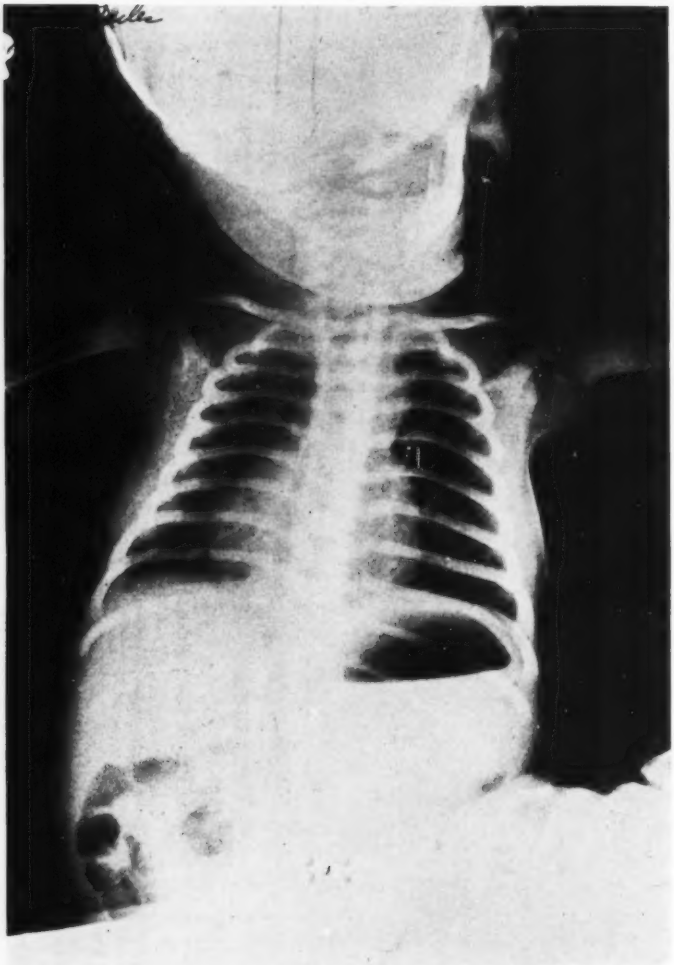

FIG. 3. R. M. X-ray of the chest taken after a single irradiation of 75 r to the mediastinum revealing mirror image dextrocardia. Note the stomach bubble to be on the left.

gestive failure. They ranged from 20 to 30 during this last admission and they are if anything decreased, indicating a depression of the respiratory center due to cerebral anoxemia.

To return to the eight questions listed above.

1. What chambers or vessels are enlarged or diminished in size?

The x-ray gives no positive information on the matter of enlargement of the ventricles or auricles. The electrocardiogram, however, shows a high peaked P wave in lead II which is rather striking considering the low voltage of the rest of the complexes. This indicates *right auricular enlargement.*

2. Is the blood supply to the body adequate or altered as to nutrition or oxygen? Also to the heart?

The blood supply appears adequate to the body as to nutrition but not as to oxygen, as evidenced by the episodes of paroxysmal dyspnea and the terminal sign of cerebral anoxemia. The low voltage of the complexes in all leads suggest that the blood supply to the heart is also poor in oxygen which in turn suggests that the coronary arteries are receiving largely venous blood, which then suggests either that the aorta is arising from the right ventricle or that the left ventricle is receiving largely venous blood.

3. Is the blood supply to the lungs adequate, diminished or excessive?

The x-rays reveal strikingly clear lung fields with greatly reduced vascular markings and it can be said rather certainly that the blood supply to the lungs is greatly reduced and that the pulmonary artery is either stenosed or absent.

4. Are great vessels both present and in normal relationship? Their branches?

Examination of the x-ray shows the shadow of the great vessels to be strikingly narrow suggested that the great vessels may be transposed. I would guess that the aortic arch was on the left which is abnormal for a dextrocardia although it frequently occurs when another malformation is present.

5. Is a venous arterial shunt present?

The presence of cyanosis and episodes of paroxysmal dyspnea indicate almost certainly that the answer to this question is yes.

6. Is an arteriovenous shunt present?

I do not believe that there is any evidence to indicate with certainty the the answer to this question.

7. Is the venous return to the heart normal?

As far as the pulmonary veins are concerned, it probably is. As far as the superior and inferior vena cava are concerned one cannot positively say without angiocardiograms.

8. Is congestive failure present?

The fact that the liver was if anything only slightly enlarged and that the respirations were not increased indicates that cerebral anoxemia and not congestive failure was responsible for the baby's death.

Now to approach the diagnosis from the point of view of statistical considerations. When dextrocardia is combined with a congenital malformation a rather unusual and complicated type of malformation can be expected. *Transposition* of the usual type can probably be ruled out. One would expect the heart to be enlarged by the age of four months and the ung fields to be congested. With the classic type of *Tetralogy of Fallot* a child usually lives a great deal longer. With a *Truncus Arteriosus* with the blood supply to the lungs by way of the bronchial arteries a characteristic contour is present even at birth and by the age of four months it should be rather striking. The countour of the heart is also not characteristic of a *Tricuspid Atresia* although this malformation with a very small auricular septal defect cannot be ruled out. No mention is made about whether the liver was pulsating.

When one turns to the rarer malformations, bearing in mind that one of these is rather likely when dextrocardia is present, one is struck with how closely extreme dextroposition of the aorta with pulmonary atresia fits in with the information available. It seems almost certain that the aorta arises from the right ventricle if only from the low voltage of the entire electrocardiogram. The right auricle is enlarged. The pulmonary artery is certainly atretic or stenosed and if it is stenosed it may be transposed. However, a single ventricle with a stenosed pulmonary artery arising from the rudimentary outlet chamber cannot be ruled out. A rare pulmonic stenosis probably cannot be absolutely ruled out.

I would list the diagnoses in order of probability as follows:

Mirror Image Dextrocardia—left aortic arch with

1. Extreme dextroposition of the aorta with pulmonary atresia or stenosis or transposition of pulmonary artery if stenosed.
2. Single ventricle with stenosed pulmonary artery arising from the rudimentary outlet chamber
3. Tricuspid atresia?
4. Pure pulmonic stenosis?

Fernando Leyva, M.D.: I would like to ask if this x-ray picture with its narrow shadow of the great vessels at the base of the heart might not be explained by the presence of a left aortic arch associated with dextrocardia.

Dr. Wedum: Yes, the occurrence of a left aortic arch with the dextrocardia would explain very well the narrowing of the great vessels shadow. As a matter of fact I believe that this is a left aortic arch, but of course we would need oblique films with barium swallow to be certain.

PATHOLOGICAL DISCUSSION

John E. Cassidy, M.D.: I am sure that we have all benefited a great deal from Dr. Wedum's most complete and interesting discussion. She has gathered together a great deal of information and organized it in such a way

that many of the complexities of this subject seem a great deal simpler to us now.

The principal findings at autopsy on this patient are as follows. The heart was markedly enlarged due mostly to hypertrophy and dilatation of the right ventricle. Its weight was 45 gms. as compared with an expected normal weight for this age of 27 gms. The aorta arose from the right ventricle in the position usually occupied by the pulmonary artery. The pulmonary artery also arose from the right ventricle, to the right of the aorta, but was much smaller than usual, measuring only 1.1 cm. in circumference. The pulmonic valve had only two cusps. The ductus arteriosus was closed; there was a narrow defect in the foramen ovale. At the base of the interventricular septum there was a defect measuring 0.6 cm. in diameter. The venous return was normal.* The heart was dextraposed with the apex lying 4 cm. to the right of the midline. There was congestion of the liver, kidneys and lungs.

The pathological diagnosis then is:

Developmental anomalies of the heart.

a. Dextrocardia
b. Abnormal origin of the aorta from the right ventricles
c. Pulmonary stenosis
d. Patent foramen ovale
e. Interventricular septal defect.

As Dr. Wedum has stated it is most likely that cerebral anoxemia was the immediate cause of death.

Dr. Wedum: I should have mentioned that a ventricular septal defect occurs in association with this malformation. The presence of the auricular septa defect I did not suspect and I do not believe on clinical grounds that one could have thought it to be present.

It should be mentioned that a hemoglobin of thirteen grams represents a marked anemia when cyanosis is present and that a few blood transfusions might have prolonged this baby's life. However, in spite of the fact that the blood supply to the lungs was inadequate, a Blalock-Taussig operation would not have benefited the child because of the difficulty the blood has in getting from the left ventricle through the ventricular septal defect over to the aorta when this vessel is so far dextroposed.

NOTES

In 1947 the Children's Hospital Staff authorized the establishment of a Tumor Board composed of representatives of the medical, surgical, radiology and pathology services. In May 1948, approximately one year after

*Although the venous return was normal, the auricles were inverted; however, as far as could be determined, the anterior venous ventricle from which both great vessels arose was the anatomical right ventricle.

its authorization, it was activated with Dr. W. Warren Sager, Chairman, representing the Surgical Department, Dr. Isidore Lattman representing the Radiology Department, Dr. E. Clarence Rice representing the Pathology Department, Dr. William Burdick representing the Medical Department and Dr. D. Joseph Judge, secretary, representing the House Staff.

The reasons for the formation of such a board are apparent when it is realized that exact knowledge as to the status of neoplastic disease in our hospital is not known. The information on the results of treatment given has not been assembled in such a manner as to be useful in determining the better forms of therapy nor have the results of following the cases after their discharge from the hospital been recorded in such a fashion as to be of the greatest value.

The material is ample and it is the purpose of the members of the Tumor Board to familiarize themselves with the available material, to study the various methods of diagnosis and treatment and follow the course of the disease in patients discharged from the hospital in an adequate manner. From the recorded observations it is hoped that progress may be made.

As organized, Dr. Judge is secretary to the board and also acts as a coordinator between the board and the attending and house staffs. The chief surgical resident functions as assistant coordinator. When a patient is seen in the Outpatient Department or Ward Service, the coordinator notifies the board who meet and examine the patient within a 24 hour period. Steps for making the diagnosis and carrying out treatment are recommended. In addition to the necessary history, physical examination, roentgen and laboratory examinations made, a photographic record of all interesting features of the case is obtained.

The board meets every Wednesday at 2:30 p.m. in the Department of Radiology. It functions in a purely consultive fashion and there is no charge for its services. Any recommendations made are carried out by the attending physician and are subject to his approval. Private patients are seen when a request is made by the physician in attendance.

Edwin B. Vaden, M.D. (*Clinico-Pathological Conference*) was born at Gretna, Virginia in 1920. He attended Hampden-Sydney College and received his M.D. from the University of Virginia. Dr. Vaden served in the United States Naval Reserve from June 1945 to December 1947 and interned at the U. S. Naval Hospital, Philadelphia, Pennsylvania. He served his externship here at Children's Hospital from January 1948 to July 1948 and at present is a resident in pathology. Upon completion of his training he plans to practise pediatrics.

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